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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/475,784	06/07/1995	PHILIP O. LIVINGSTON	43016-C/JPW/	4174

7590 08/27/2002

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	54

DATE MAILED: 08/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/475,784	Applicant(s) LIVINGSTON ET AL.	
	Examiner Anne Holleran	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *78-93 and 95-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78-93 and 95-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed April 30, 2002 is acknowledged. Claims 78, 93 and 95 were amended.

2. Claims 78-100 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections / Rejections Maintained:

4. The prior objection to the disclosure is maintained for the reasons as set forth in the Office Action mailed 6/10/96 (see Paper No. 9).

Applicants submit they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. Until applicants submit a proper Figure said objection is maintained.

5. Claims 78, 80-92 and 94-99 are provisionally rejected under the judicially created doctrine of obviousness-type, double patenting as being unpatentable over the claims 78, 80-92, 94, and 96-99 of copending Application No. 08/477,097 4 for reasons already made of record in Paper No. 23, mailed 10-5-99 and in paper #25, mailed 6-19-2000.

Applicant argues that the claims of 08/477,097 do not render obvious the instant claims. Applicant's arguments filed 6/10/96 have been fully considered but they are not persuasive,

because applicant has provided no reasoning to dispute the obviousness set forth in previous office actions.

6. Claims 78 and 80-92 and 94-99 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 109-122 of copending Application No. 08/477,147 for reasons already made of record in Paper No. 23, mailed 10-5-99 and in paper #25, mailed 6-19-2000.

Applicant argues that the claims of 08/477,147 do not render obvious the instant claims. Applicant's arguments filed 6/10/96 have been fully considered but they are not persuasive, because applicant has provided no reasoning to dispute the obviousness set forth in previous office actions.

7. Claims 78, 80-92 and 94-99 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 97-99, 101-111, and 113-118 of copending Application No. 08/196,154 for reasons already made of record in Paper No. 23, mailed 10-5-99 and in paper #25, mailed 6-19-2000.

Applicant argues that the claims of 08/196,154 do not render obvious the instant claims. Applicant's arguments filed 6/10/96 have been fully considered but they are not persuasive, because applicant has provided no reasoning to dispute the obviousness set forth in previous office actions.

Claim Rejections Withdrawn:

8. The rejection of claims 78-81, 83-93 and 95-100 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment.

9. The rejection of claims 78-93, 95 and 97-99 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol, 182:32-43, 1990), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976) is withdrawn in view of the amendment.

10. The rejection of claims 96 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol, 182:32-43, 1990), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976 further in view of Irie et al. (U.S. Patent Nol 4,557,931), is withdrawn in view of the amendment.

New Grounds of Rejection:

11. Claims 78-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiegand et al (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989) in view of Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988), Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976).

Wiegand discloses modified glycosphingolipids (GM3, GD3, GM2 and GM1). Wiegand discloses a method for chemical modification of the sphingoid portions of glycosphingolipids to make glycosphingolipids capable of coupling to proteins (see abstact). Wiegand discloses that the method of chemical modification is that of ozonolysis at the C-4 double-bond of the sphingosine base resulting in the formation of a reactive aldehyde species (col. 2, line 43 - col. 3, line 67). Wiegand discloses that the aldehyde group is susceptible to reductive amination. Wiegand fails to disclose conjugation of the modified glycosphingolipid to KLH via an amine linkage between the C-4 carbon of sphingosine base and an ε-aminolysyl group of KLH. Wiegand also fails to disclose a composition that comprising a saponin derivable from the bark of the Quillaja saponaria Molina Tree (QS-21).

Fiume (1988) teaches that reductive amination of reactive aldhehyde species with proteins having ε-lysine groups is well known in the art (see page 268-269). Specifically, Fiume teaches that aldehyde group of a galactosyl residue may be reacted with an ε-lysine of a protein.

Ritter (1991) teaches that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help

necessary for the response (page 406, paragraph 1). Ritter teaches that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissues, c) is able to mediate antibody-dependent cell-mediated cytotoxicity, d) and is generally detectable in the serum for longer periods after immunization.

Kensil et al teach that QS-21 (i.e. the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response than conventional aluminum hydroxide (page 433, column 2, paragraph 4, and Figure 3). Kensil et al also teach that the immune responses obtained with QS-21, reached a plateau at doses between 10-80 ug in mice (page 433, column 1, paragraph 3).

Maricani et al teach the use of QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (page 93, paragraph 1).

Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity of the ganglioside derivative with antibodies.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the modified glycosphingolipids of Wiegand to make glycoconjugates that are the same as those claimed. Weigand teaches a modified glycosphingolipid that has a reactive aldehyde group (at the C-4 position of the sphingosine base) that may be used for coupling to proteins as taught by Fiume, because Fiume demonstrates that methods of reductive amination to link proteins, via ε-lysine residues, to reactive aldehyde groups is known in the art. Because Wiegand teaches a method of ozonlysis that results in the formation of a reactive aldehyde species, the bond that would be formed between the C-4 carbon

of the sphingosine base and the KLH would be an amino linkage that would cause the C-4 carbon to be present in a CH_2 group. It would have been further prima facie obvious to one of ordinary skill in the art to have used KLH as the protein carrier because, as Ritter teaches, attachement of gangliosides to carrier proteins such as KLH increase IgG responses to gangliosides. It would have been prima facie obvious to one of ordinary skill in the art to add QS-21, because, as taught by Kensil, it provides for a higher antibody response, and QS-21 provides the advantages that it is not toxic to animals (see Marciani).

It also would have been prima facie obvious to optimize the doses of QS-21 in the composition, also it would have been prima facie obvious to one of ordinary skill in the art to optimize the weight ratio of the components of the composition to provide an optimal response.

One would have reasonably expected the conjugation procedure to work as substituted because conjugation through the e-aminolysyl groups of carrier proteins for enhance immunogenicitiy is routine in the art and, as Uemura (1976) teaches, ozonolysis and reduction of various sphingolipids does not affect the haptenic reactivity with antibodies.

12. Claims 78, 93, 95-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiegand et al (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989), Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988) Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976).

As discussed above, Wiegand in combination with Fiume teaches a glycoconjgate as claimed in claim 78.

Livingston teaches that melanoma recurrence was delayed in patients developing GM2 antibodies after treatment with the composition (page 7048, paragraph 1 and column 2, paragraph 2). Livingston et al teach that more patients produced IgM antibodies than IgG antibodies to the GM2 (pate 7047, paragraph bridging columns 1-2). Livingston et al also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (page 7045, column 1, paragraph 2).

Ritter (1991) teaches that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (page 406, paragraph 1). Ritter teaches discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissues, c) is able to mediate antibody-dependent cell-mediated cytotoxicity, d) and is generally detectable in the serum for longer periods after immunization.

Livingston et al (U.S. Patent No. 5, 102,663) teach that gangliosides GM3, GM2, GD3, GD2, GT3 and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin (column 1, lines 22-28).

Kensil et al teach that QS-21 (i.e. the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response than conventional aluminum hydroxide (page 433, column 2, paragraph 4, and Figure 3). Kensil et al also teach that

the immune responses obtained with QS-21, reached a plateau at doses between 10-80 ug in mice (page 433, column 1, paragraph 3).

Maricani et al teach the use of QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (page 93, paragraph 1).

Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity of the ganglioside derivative with antibodies.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the modified glycosphingolipids of Wiegand to make glycoconjugates that are the same as those claimed, and then to have used the glycoconjugates in compositions for the stimulating or enhancing antibody production or in a method of treating cancer, because Livingston teaches that melanoma recurrence is delayed in patients developing GM2 antibodies after treatment with vaccines comprising GM2 (page 7048, paragraph 1 and column 2, paragraph 2). Livingston et al teach that more patients produced IgM antibodies than IgG antibodies to the GM2 (page 7047, paragraph bridging columns 1-2). Livingston et al also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (page 7045, column 1, paragraph 2). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have added QS-21 as an adjuvant to the GM-2-KLH conjugate for use as a vaccine because the conjugated composition would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991), thus providing the advantages by Ritter et al (1991) and, as Kensil teaches, adding the QS-21 is advantageous because it provides for a higher antibody response that the

commonly used adjuvant . Also, QS-21 provides the advantages that it is not toxic to animals (see Marciani).

It also would have been prima facie obvious to optimize the doses of QS-21 in the composition, also it would have been prima facie obvious to one of ordinary skill in the art to optimize the weight ratio of the components of the composition to provide an optimal response.

One would have reasonably expected the conjugation procedure to work as substituted because conjugation through the e-aminolysyl groups of carrier proteins for enhance immunogenicitiy is routine in the art and, as Uemura (1976) teaches, ozonolysis and reduction of various sphingolipids does not affect the haptenic reactivity with antibodies.

It also would have been prima facie obvious to one of ordinary skill in the art to substitute any one of GM3, GD2, GD3, or O-acetyl GD3 for the GM2 ganglioside in the composition and method as combined supra because they are all prominent cell-membrane components of melanomas as taught by Livingston et al (U.S. Patent No. 5,102,663). Optimization of the dosage, route of immunization, number of sites of immunization to administer the composition is will within the skill of the ordinary artisan.

One would have reasonably expected the conjugation procedure to work as substituted because conjugation through the e-aminolysyl groups of carrier proteins for enhance immunogenicitiy is routine in the art and Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies.

13. The rejection of claim 96 under 35 U.S.C. 103(a) as being unpatentable over Wiegand et al (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989), in view of Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988) Livingston et al. (Cancer Research, 149:7045-7050, 1989), Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976) as applied to claims 78, 80-92, 94 and 96-99 above and further in view of Irie et al. (U.S. Patent Nol 4,557,931).

The teachings of Wiegand , Fiume, Livingston et al.(1989), Ritter et al. (1991), Livingston et al. (U.S. Patent No. 5,102,663), Kensil (1991), Marciani (1991) and Uemura (1976) are discussed above. The combination differs by not teaching the administration of the composition for treating cancer of epithelial origin.

Irie et al teaches that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas (column 1, lines 28-31).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer the GM-2-KLH conjugate/ QS-21 composition or other ganglioside conjugate/QS-21 composition as combined supra to patients afflicted with or susceptible to a recurrence of cancer of an epithelial origin (i.e. breast carcinomas) because the ganglioside GM-2 is found in the stroma of the tumor as taught by Irie et al and one of ordinary skill in the art would expect that the antibodies produced by the composition react with the tumor and treat the disease.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
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August 26, 2002

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